JC07 Rec'd PCT/PTO 28 DEC 2001

BAKER BOTTS L.L.P

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35.U.S.C. 371

EXPRESS MAIL LABEL No	DATE
ET 544 763 265 US	December 28, 2001

ATTORNEY'S DOCKET NO: 34894-PCT-USA (072745.0128)

U S APPLICATION NO: To be assigned 10/019613

INTERNATIONAL APPLICATION NO	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/GB00/02551	3 July 2000	2 July 1999

TITLE OF INVENTION: USE OF CORTISOL ANTAGONISTS IN THE TREATMENT FOR HEART FAILURE

APPLICANT(S) FOR DO/EO/US: Cortendo AB

Applicant herewith submits to the United States Designated /Elected Office (DO/EO/US) the following items and other information:

1. ☑ This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.
3. [ ] This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(I).
4. ☑ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☑ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☑ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] has been transmitted by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [ ] A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☑ A copy of the International Search Report (PCT/ISA/210)
   a. ☑ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been transmitted by the International Bureau
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [ ] have not been made and will not be made.
8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. [ ] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [ ] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. ☑ A copy of the International Preliminary Examination Report (PCT/IPEA/409)
12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☑ A FIRST preliminary amendment.
    [ ] A SECOND or SUBSEQUENT preliminary amendment.
14. [ ] A substitute specification.
15. [ ] A change of power of attorney and/or address letter.
16. [ ] Other items or information:
    a. [ ] a copy of the International Search Report (PCT/ISA/210)
    b. [ ] a copy of the International Preliminary Examination Report (PCT/IPEA/409)
    c. PCT Application No. PCT/GB00/0255 was published in English under Publication No. WO 01/01871 A1 on 11 January, 2001.
    d. Information Disclosure Statement
    e. PTO Form 1449
    f. Copies of References Listed in Information Disclosure Statement and Form 1449
    g. Check for $860.00
    h. Return receipt postcard

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INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/GB00/02551 10/019613	3 July 2000	2 July 1999

17. [ ] The following fees are submitted:

Basic National Fee (37 CFR 1.492(a)(1)-(5):

Neither international preliminary examination fee (37 CFR 1.482)

Nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO (1.492(a)(3)) $1,000.00

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO (1.492(a)(5) $860.00

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO(1.492(a)(2)) $710.00

International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) (1.492(a)(1)) $690.00

International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) $ 100.00

CALCULATIONS PTO USE ONLY

ENTER APPROPRIATE BASIC FEE AMOUNT =				$ 860	
Surcharge of $130.00 for furnishing the oath or declaration later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 C.F.R. 1.492)(e)).				$	
Claims	**Number Filed**	**Number Extra**	**Rate**	$	
Total Claims	9 -20=	0	X $ 18.00	$ 0	
Independent Claims	3 -3=	0	X $ 80.00	$ 0	
Multiple dependent claim(s) (if applicable)			+ $270.00	$	
TOTAL OF ABOVE CALCULATIONS =				$ 860	
Reduction by ½ for filing by small entity, if applicable.				$	
SUBTOTAL =				$ 860	
Processing fee of $130.00 for furnishing the English translation later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(f)). +				$	
TOTAL NATIONAL FEE =				$ 860	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40.00 per property +				$	
TOTAL FEES ENCLOSED =				$ 860	
				Amt. refunded	$
				charged	$

a. [✓] A check in the amount of $ 860.00 to cover the above fees is enclosed.

b. [ ] Please charge our Deposit Account No. 02-4377 in amount of $_____ to cover the above fees. A copy of this sheet is enclosed.

c. [✓] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 02-4377. A copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:
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Rochelle K. Seide

Attorney: Rochelle K Seide, Ph.D PTO Reg: 32,300

December 28, 2001
Date

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BAKER BOTTS L.L.P.

Attorney Docket Number: 34894-PCT-USA (072745.0128)

Title: USE OF CORTISOL ANTAGONISTS IN THE TREATMENT FOR HEART FAILURE

Use Space Below for Additional Information:

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34894-PCT-USA (072745.0128)
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Cortendo AB		
Serial No.	:	Not Yet Assigned	Authorized Officer:	Not Yet Assigned
Filed	:	January 2, 2002	Group Art Unit:	Not Yet Assigned
For	:	USE OF CORTISOL ANTAGONISTS IN THE TREATMENT OF HEART FAILURE		

I hereby certify that this paper is being deposited with the United States Postal Service as Express Mail No. ET 544 763 265 US addressed to: Commissioner for Patents, Arlington, VA 22202

December 28, 2001
Date of Deposit

~~Rochelle~~ K. Seide
Attorney Name

32,200
PTO Registration No.

Signature

December 28, 2001
Date of Signature

PRELIMINARY AMENDMENT

Hon. Commissioner for Patents and Trademarks
U.S. Patent and Trademark Office
P.O. Box 2327
Arlington, VA 22202

Sir:

Prior to the Examination of the present application, please make the following amendments.

IN THE TITLE:

Please amend the title to read as follows:

USE OF CORTISOL ANTAGONISTS IN THE TREATMENT OF HEART FAILURE

IN THE SPECIFICATION:

Please insert the following text before the first paragraph of the specification:

--CROSS REFERENCES TO RELATED APPLICATIONS

This application is a national stage filing of International Patent Application PCT/GB00/02551, filed 3 July 2000, which claims priority from Great Britain Patent Application 9915625.9, filed 2 July 1999.--

Please insert the following text into the specification on page 18.

--ABSTRACT OF THE DISCLOSURE

The present invention relates to the use of a cortisol antagonist in the manufacture of a medicament for the treatment of heart failure as well as to a method of treating heart failure which comprises administration of a cortisol antagonist and to a product containing (a) a cortisol antagonist and (b) a second drug as a combined preparation for simultaneous, separate or sequential use in the treatment of heart failure or in improving cardiac function and reducing exercise intolerance.--

IN THE CLAIMS:

Please cancel original Claims 1-12.

Please add the following new Claims 13-21:

--13. (New) A method for the treatment of a cardiac pathology in a mammal which comprises administering a cortisol antagonist to said mammal in an amount effective to treat the

cardiac pathology.

14. (New) The method of claim 13 wherein the cardiac pathology is selected from the group consisting of congestive heart failure, diastolic heart failure, low-output heart failure, right-sided heart failure, cardiac hypertrophy, and cardiac fibrosis.

15. (New) The method of claim 14 wherein the cortisol antagonist is an inhibitor of cortisol synthesis.

16. (New) The method of claim 15 wherein the inhibitor of cortisol synthesis is ketoconazole or a derivative thereof.

17. (New) The method of claim 16 wherein the cortisol synthesis inhibitor is a Cis-2S,4R and/or Cis-2R,4S isomer of ketoconazole.

18. (New) A composition for daily administration to a mammalian subject comprising:

i) a cortisol antagonist, and

ii) a second drug,

as a combined preparation for simultaneous, separate or sequential use in the treatment of heart failure or in improving cardiac function and reducing exercise intolerance.

19. (New) A method for the treatment of one or more symptoms associated with heart failure selected from the group comprising edema of lower limbs, pulmonary edema, dyspnea, liver enlargement, increased heart rate, reduced stroke volume, shortness of breath and exercise intolerance which comprises administering the composition of claim 18 to a mammalian subject.

20. (New) The method of claim 19 wherein the symptom is pulmonary edema.

21. (New) The composition of claim 18 wherein the daily dose of the cortisol antagonist to a subject being treated is 100-200 mg.--

REMARKS

Prior to examination of the above-captioned application, Applicants respectfully request consideration of this amendment and remarks made herein. Claims 1-12 are pending. Claims 1-12 have been cancelled and Claims 13-21 have been added to more clearly state the subject matter of the invention. The specification has been amended to include cross-reference to related applications and to include an abstract of the disclosure on a separate page following the claims. No new matter has been added by the amendments made to the specification or the claims.

In accordance with 37 C.F.R. § 1.121, Applicant has provided (1) accurate instructions to amend the specification and claims, (2) a substitute specification and amended claims in clean form herein, and (3) another version of the substitute specification and amended claims marked up to show all the changes relative to the previous version of the claims.

Applicants request an early and favorable consideration of Claims 13-21.

Respectfully submitted,

BAKER BOTTS L.L.P.

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New York, N.Y. 10112-0228

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MARKED UP VERSION OF TECHNICAL AMENDMENTS

IN THE TITLE:

Please amend the title as follows:

USE OF CORTISOL ANTAGONISTS IN THE TREATMENT OF[FOR] HEART FAILURE

IN THE SPECIFICATION:

Please insert the following text before the first paragraph of the specification:

--CROSS REFERENCES TO RELATED APPLICATIONS

This application is a national stage filing of International Patent Application PCT/GB00/02551, filed 3 July 2000, which claims priority from Great Britain Patent Application 9915625.9, filed 2 July 1999.--

Please insert the following text into the specification on page 18:

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The present invention relates to the use of a cortisol antagonist in the manufacture of a medicament for the treatment of heart failure as well as to a method of treating heart failure which comprises administration of a cortisol antagonist and to a product containing (a) a cortisol antagonist and (b) a second drug as a combined preparation for simultaneous, separate or sequential use in the treatment of heart failure or in improving cardiac function and reducing exercise intolerance.--

IN THE CLAIMS:

Please cancel original Claims 1-12.

Please add the following new Claims 13-21:

--13. (New) A method for the treatment of a cardiac pathology in a mammal which comprises administering a cortisol antagonist to said mammal in an amount effective to treat the cardiac pathology.

14. (New) The method of claim 13 wherein the cardiac pathology is selected from the group consisting of congestive heart failure, diastolic heart failure, low-output heart failure, right-sided heart failure, cardiac hypertrophy, and cardiac fibrosis.

15. (New) The method of claim 14 wherein the cortisol antagonist is an inhibitor of cortisol synthesis.

16. (New) The method of claim 15 wherein the inhibitor of cortisol synthesis is ketoconazole or a derivative thereof.

17. (New) The method of claim 16 wherein the cortisol synthesis inhibitor is a Cis-2S,4R and/or Cis-2R,4S isomer of ketoconazole.

18. (New) A composition for daily administration to a mammalian subject comprising:

i) a cortisol antagonist, and

ii) a second drug,

as a combined preparation for simultaneous, separate or sequential use in the treatment of heart failure or in improving cardiac function and reducing exercise intolerance.

19. (New) A method for the treatment of one or more symptoms associated with heart failure selected from the group comprising edema of lower limbs, pulmonary edema, dyspnea,

liver enlargement, increased heart rate, reduced stroke volume, shortness of breath and exercise intolerance which comprises administering of the composition of claim 18 to a mammalian subject.

20. (New) The method of claim 19 wherein the symptom is pulmonary edema.

21. (New) The composition of claim 18 wherein the daily dose of the cortisol antagonist to a subject being treated is 100-200 mg.--

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USE OF CORTISOL ANTAGONISTS IN THE TREATMENT FOR HEAT FAILURE

The present invention relates to heart failure and in particular to the use of a particular class of compounds for the treatment of heart failure.

Heart failure, which is generally characterised by impaired cardiac function and exercise intolerance affects a very large number of people worldwide, particularly in the Western world. Heart failure and its complications are responsible for premature death in a proportion of sufferers and generally curtails the working life and range of activities which can be undertaken by the sufferer, as well significantly reducing overall quality of life. Heart failure is found in both sexes, young and old but is particularly prevalent in males and elderly or middle aged people.

Heart failure may be caused by a number of different underlying heart diseases. Heart diseases and events which may be a factor in causing heart failure include valvular heart disease, valvular stenosis, heart muscle disease, myocardial ischemia or infarction, cardiomyopathia and infiltrative process or inflammatory process of either the muscle, endocardium or epicardium of the heart.

As heart failure is a common and serious condition, significant efforts have been made by the medical community towards developing treatments for heart failure. A successful treatment should improve quality of life, prevent or slow progression of cardiac dysfunction and prolong life. Non-pharmacological treatments include modified diets to reduce sodium retention and cause weight loss and exercise programmes, although there is a conflict between the need to improve ventricular performance which is aided by bed rest and a desire to improve exercise intolerance and maintain conditioning which is favoured by a moderate exercise

regime. In some cases heart failure will be treated by surgical means including full heart transplantation.

A number of pharmaceuticals are available for the treatment of heart failure and for the most part these fall into three broad categories, diuretics, vasodilators and inotropic drugs. Diuretic therapy seeks to maintain intravascular volume at the lowest level compatible with optimal cardiac performance. A reduction in intravascular volume has the advantage of reducing interstitial fluid by allowing its reabsorption into the vascular space. Furosemide and/or metolazone have been used as diuretics in the treatment of heart failure but the use of these and other diuretics may lead to an undesirable drop in intracellular potassium levels. Potassium levels should be monitored and potassium supplementation may be required.

Vasodilator drugs may be useful in increasing stroke volume due to a reduction in vascular impedance and in reducing preload due to an increase in venous capacitance. Optimal treatment using vasodilators will often require coadministration of an arterial dilator such a hydralazine or minoxidil and a venodilator such as isosorbide dinitrate.

Treatment with a diuretic and/or vasodilator may be supplemented by an inotropic drug such as digoxin, dobutamine or aminone.

In addition, a patient suffering from heart failure may, in certain circumstances be prescribed antiarrhythmic drugs, β-adrenoreceptor blockers, anticoagulants, an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II antagonist.

While a large number of pharmaceuticals are available to the physician for treating heart failure, different patients will have different needs and successful treatment will often require administration of a range of complementary drugs. Adverse reactions by some patients to particular drugs and drug intolerance

means there is a continuing demand for new drugs of use in the treatment of heart failure, as physicians strive to find the best drug or combination of drugs for each sufferer. Moreover, heart disease is so widespread that the public and doctors alike demand ever more effective methods of treatment which can provide a higher quality of life for longer periods.

It has now surprisingly been found that administration of a cortisol antagonist is effective in the treatment of heart failure and symptoms associated with heart failure.

Thus, in one aspect, the present invention provides the use of a cortisol antagonist for the manufacture of a medicament for the treatment of heart failure.

'Heart failure' can be defined clinically as a syndrome of ventricular dysfunction accompanied by reduced exercise capacity. Typically, there is a characteristic pattern of hemodynamic, renal and neural responses. In effect, heart failure is the inability of the heart to pump blood at an adequate rate to fulfill tissue metabolic requirements or the ability to do so only at an elevated filling pressure. Heart failure typically results in an inability to drain away body fluid which may cause ascites (body fluid in abdominal cavity), this often being observed in backward heart failure and when the liver is swollen. Within this general definition, it is intended to include the following types of heart failure and cortisol antagonists are suitable for use in treating all of these:

Acute congestive heart failure, a rapidly occurring deficiency in cardiac output marked by venocapillary congestion, hypertension and oedema, usually pulmonary oedema.

Backward heart failure, a concept of heart failure stating that imbalance of performance of the ventricles due to dysfunction of one results in a rise in pressure

behind that ventricle, with backward transmission of the increased pressure and consequent rise in venous pressure and distension.

Congestive heart failure (CHF), a clinical syndrome due to heart disease, characterised by breathlessness and abnormal sodium and water retention, often resulting in oedema. The congestion may occur in the lungs or peripheral circulation or both, depending on whether the heart failure is right-sided or general.

Diastolic heart failure, heart failure due to a defect in ventricular filling caused by an abnormality in diastolic function.

Forward heart failure, a concept of heart failure that emphasizes the inadequacy of cardiac output relative to body needs; oedema is attributed primarily to renal retention of sodium and water, and venous distention is considered a secondary feature.

High-output heart failure, heart failure in which the cardiac output remains high enough to maintain a brisk circulation with warm extremities but is inadequate to meet demand; it is most often associated with hyperthyroidism, anemia, arteriovenous fistulas, beriberi, osteitis deformans or sepsis.

Left-sided heart failure, left ventricular failure, failure of adequate output by the left ventricle despite an increase in distending pressure and in end-diastolic volume, with dyspnea, orthopnea and other signs and symptoms of pulmonary congestion and oedema.

Low-output heart failure, heart failure in which cardiac output is decreased, as in most forms of heart disease, leading to clinical manifestations of impaired peripheral circulation and peripheral vasoconstruction (cold, pale extremities, cyanosis, narrowed pulse pressure).

Right-sided heart failure, right ventricular failure, failure of proper functioning of the right ventricle, with venous engorgement, hepatic enlargement,

and subcutaneous oedema; it is often combined with left-sided heart failure.

Systolic heart failure, heart failure due to a defect in expulsion of blood caused by an abnormality in systolic function.

A cortisol antagonist is particularly well suited to the treatment of congestive, diastolic, backward, low-output and right-sided heart failure. Thus, the treatment of these conditions represents a preferred aspect of the present invention.

According to the New York Functional Classifications (Ganiats, T.G., Browner, D.K., Dittrich, H.C. in American Heart Journal (1998) 135: 5 Pt 1, 819-824) the severity of heart failure can be divided into four classes as follows:

Class I - no limitation of physical activity: ordinary physical activity does not cause undue fatigue, shortness of breath or palpitation;

Class II - slight limitation of physical activity; such patients are comfortable at rest, ordinary physical activity results in fatigue, shortness of breath, palpitations or angina;

Class III - marked limitation of physical activity; although patients are comfortable at rest, less than ordinary activity will lead to symptoms;

Class IV - inability to carry out any physical activity without discomfort: symptoms of congestive heart failure are present even at rest. With any physical activity increased discomfort is experienced.

Cortisol antagonists are suitable for the treatment of all classes of heart failure, particularly classes II to IV.

By 'cortisol antagonist' is meant any compound or agent which reduces production of cortisol or circulating levels of biologically active cortisol or which limits the biological effects of cortisol by inhibiting cortisol (glucocorticoid) receptors

competitively or non-competitively, or in any other way. The term includes agents which interfere with the regulation of cortisol synthesis along the so-called hypothalmic-pituitary-adrenal gland (HRA) axis. Thus a "cortisol antagonist" may broadly be regarded as any compound or agent which antagonises or inhibits (i.e. reduces or prevents) cortisol activity.

A large number of agents are known to suppress glucocorticoid production or inhibit their receptor binding in humans: sodium valporate (Aggernaes, H. et al. Acta Psychïatr. Scand. (1988) 77 170-174); Enkephalins and their synthetic analogues (Stubbs, W.A. et al. The Lancet (1978) 1225-1227); Opioids such as loperamide, commercially available under the trademark IMODIUM from Janssen Pharmaceutica N.V.; the antihypertensive drug Clonidine (Slowinska-Srzednicka, J. et al. European Journal of Clinical Pharmacology (1988) 35 115-121); Oxytocin (Legros, J.J. et al. Endocrinologica (1987) 114 345-349) and Mifepristone, known as RU 486 or RU 38486 available from Roussel-Uclaf. Mifepristone and other antagonists which operate at the receptor level are a class of preferred active agents for use in the present invention.

Any of the above agents or any of the large number of cortisol synthesis inhibitors known in the art, e.g. econazole (Squibb, U.K.), ketoconazole and miconazole (Janssen, Belgium) and their derivatives, may be used as cortisol antagonists according to the present invention. In the case of econazole and miconazole, derivatives of these particular compounds are preferred.

'Derivatives' encompass compounds which are structurally related to the primary compound (e.g. ketoconazole) but are functionally equivalent or superior. Thus, a derivative might have a slightly inferior therapeutic activity but be a useful molecule because it exhibits reduced toxicity, is more convenient to formulate or administer etc. Derivatives may include

salts or other variants which have been more significantly modified while retaining functionally important structural motifs in common with the primary compound. In the case of econazole and miconazole, such derivatives may exhibit better overall properties than the primary compounds in terms of therapeutic activity and toxicity, for example.

Preferred cortisol antagonists include those compounds which inhibit the synthesis of cortisol, either by reducing the production of cortisol in any form or which cause the production of a modified form of cortisol which is less biologically active than native, naturally occurring cortisol. Preferably, cortisol synthesis inhibitors will act on the cortisol synthetic pathway in a way which does not significantly affect the normal production of the other steroid hormones, in particular which does not significantly effect production of mineralocorticoids such as aldosterone. The 'significance' of the effect is considered in terms of the biological, *in vivo*, effect. Ketoconazole and its derivatives are preferred for use according to the invention and in addition, isomers of ketoconazole are known and may be used, individually or in combination (Rotstein et al., J. Med. Chem. (1992) 35, 2818-2825). The Cis-2S,4R and Cis-2R,4S isomers are particularly preferred for use in accordance with the present invention. These isomers may be used individually or in combination as in the commercially available product Fungoral™ (Janssen-Cilag, Belgium).

In the case of cortisol antagonists which act via cortisol (glucocorticoid) receptors, the antagonist will preferably have an effect on the receptors in the kidney and/or the heart. The binding affinity which an antagonist has for receptors in different organs may not be uniform and preferably the antagonist used in the present invention will have a comparatively higher binding affinity for the glucocorticoid receptors in the

heart and/or kidney.

The cortisol antagonists for use according to the present invention have a sufficiently negative effect on circulating levels of biologically active cortisol or on its biological efficacy to cause a measurable and significant improvement in heart failure or its associated symptoms. It is not expected that in all cases treatment will be totally successful but "treatment" according to the present invention should include improvement in one or more of the following areas: fluid retention including oedema of lower limbs and fluid in the lungs (pulmonary oedema), dyspnea, liver enlargement, heart rate, stroke volume, shortness of breath, exercise intolerance and general physical and mental health. Particularly, improvements are seen in symptoms associated with fluid retention (e.g. liver enlargement, peripheral and pulmonary odema and ascites).

Advantageously, according to the uses and method of the present invention, one or more of the following benefits may be achieved:

a 10% or more reduction in liver size,

a 10% or more reduction in heart rate,

a 15% or more improvement in physical health according to the test described in the Examples herein.

Further symptoms which often occur with heart failure, whatever the cause, are enlargement of the heart and development of a fibrosis in the heart muscle. These morphological aspects of heart failure can also be treated successfully by administration of a cortisol antagonist.

Heart failure will be diagnosed when a patient has impaired cardiac function and exercise intolerance. All patients with heart failure, whether newly diagnosed or at a more advanced stage can be considered for treatment in accordance with the present invention. Treatment with a cortisol antagonist may be successful whatever

the underlying disease which has resulted in a diagnosis of heart failure. The observations which have resulted in the present invention relate to the treatment of heart failure itself and its symptoms not to the diseases and risk factors which may give rise to heart failure. Various medical conditions such as cardiovascular disease may or may not lead to heart failure but as the implications for untreated heart failure are serious, it is beneficial to have available treatments specifically for heart failure and its associated symptoms.

Thus, in a further aspect is provided a method of treating heart failure in a mammal which method comprises administering a pharmaceutically effective amount of a cortisol antagonist to said mammal.

Alternatively viewed, according to the method of the invention, an amount of cortisol antagonist is administered which is effective to improve one or more of the symptoms of heart failure; these areas in which improvement may be observed are discussed above.

A 'pharmaceutically effective' amount can be determined with reference to the various areas discussed herein in which treatment may provide measurable improvements, and selected with reference to the Examples and standard practices for deciding dosage amounts.

Generally, patients in need of such a treatment will be diagnosed as suffering from heart failure by reference to the clinical definitions provided herein or other medically accepted criteria.

The cortisol antagonist or antagonists may be administered to the patient in any convenient form, orally or by intravenous, enteral or parenteral routes. Preferably the cortisol antagonist will be administered by oral routes.

Alternatively viewed, the invention provides a method of improving cardiac function and reducing

exercise intolerance in a mammal which method comprises administering a pharmaceutically effective amount of a cortisol antagonist to said mammal.

Likewise, the invention provides the use of a cortisol antagonist in the production of a medicament for improving cardiac function and reducing exercise intolerance.

An improvement in cardiac function may include a reduction in heart rate and/or an increase in stroke volume. Exercise intolerance is generally characterised by breathlessness and other signs of fatigue, cramp etc., primarily due to an inability of the patient suffering from heart failure to supply sufficient oxygenated blood to muscle and other organs and tissue. It can be measured by a subnormal physical exercise test (Faggiano, P., D'Aloia, A., Gualeni, A. and Giordano, A. American Journal of Cardiology (1998) 15 81:4, 437-42).

Compositions comprising a cortisol antagonist as defined above are preferably formulated prior to administration.

The present invention therefore also provides a pharmaceutical composition for use in the treatment of heart failure, said composition comprising a cortisol antagonist together with at least one pharmaceutically acceptable carrier, diluent or excipient. The active ingredient in such compositions may comprise from 0.05% to 99% by weight of the formulation, more preferably 0.1% to 1.0%.

By "pharmaceutically acceptable" is meant that the ingredients must be compatible with other ingredients of the composition as well as physiologically acceptable to the recipient.

The pharmaceutical compositions may be formulated according to any of the conventional methods known in the art and widely described in the literature. Thus, the active ingredient may be incorporated, optionally together with other active substances, with one or more

conventional carriers, diluents and/or excipients, to produce conventional galenic preparations such as tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments, soft and hard gelatin capsules, suppositories, sterile injectable solutions sterile packaged powders, and the like.

Examples of suitable carriers, excipients, and diluents are lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, aglinates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water syrup, water, water/ethanol, water/ glycol, water/polyethylene, glycol, propylene glycol, methyl cellulose, methylhydroxybenzoates, propyl hydroxybenzoates, talc, magnesium stearate, mineral oil or fatty substances such as hard fat or suitable mixtures thereof. The compositions may additionally include lubricating agents, wetting agents, emulsifying agents, suspending agents, preserving agents, sweetening agents, flavouring agents, and the like. The compositions of the invention may be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art. Sustained and/or delayed release formulations may be particularly convenient.

The active agents are preferably formulated into tablets, each tablet containing a predetermined amount of active ingredient.

Suitable doses will vary from patient to patient and can be determined by the physician in accordance with the weight, age and sex of the patient and the severity of the condition and also the particular antagonist selected. A typical total daily dose will be in the region of 50 or 100-1200 mg of a cortisol

antagonist which may be administered as a single dose or in several smaller doses during the day. Typical single doses will be in the region of 100-800 mg. Administration may advantageously be at around 10.00 p.m. in order to reduce cortisol activity during the night when natural cortisol levels are at their highest. Ketoconazole is preferably administered as a daily dose of 200-1000 mg, e.g. 300-600 mg.

During the majority of the treatment period, typically 75% or more, effective treatment will be daily. By 'effective treatment' is meant that the circulating levels of the cortisol antagonist are at physiologically effective levels; this may be achieved by daily administration or, for example, by use of a controlled-released formulation which offers sustained release over several days or more.

Improvements in patients treated in accordance with the present invention may be seen immediately or after some (e.g. 2-4) weeks and treatment should normally be continued for 3 months or more to achieve maximum benefits. As with most treatments for heart failure, it may be necessary to administer the cortisol antagonist for the rest of the patient's life. Such long term treatment may not necessarily be continuous and the optimum dose may vary during the course of treatment.

Use of a cortisol antagonist may be in place of or in addition to use of other drugs for the treatment of heart failure. This may improve the efficacy of the overall treatment regime and/or reduce the amount of drugs required by the patient or enable the physician to cease administration of a drug which is causing undesirable side effects.

As well as treatments which comprise the co-administration of a cortisol antagonist and one or more other drugs for the treatment of heart failure, medicaments and treatments in accordance with the present invention may comprise more than one cortisol

antagonist. Treatment may involve administration of an antagonist which affects synthesis of cortisol in the adrenal glands and also treatment with an antagonist which inhibits the activity of cortisol at the receptor level. Furthermore treatment may involve administration of an antagonist which operates along the HPA axis as mentioned above.

Thus, in a further aspect the present invention provides a product containing (a) a cortisol antagonist and (b) a second drug (e.g. a second agent effective in the treatment of heart failure) as a combined preparation for simultaneous, separate or sequential use in the treatment of heart failure or in improving cardiac function and reducing exercise intolerance.

Suitable 'second drugs or agents' include known drugs for use in the treatment of heart failure as are discussed above e.g. diuretics, vasodilators, inotropic drugs, ACE inhibitors and angiotensin II antagonists and also a second cortisol antagonist as defined herein.

Where two or more active agents are administered, they may be given simultaneously to the patient or times of administration may be staggered throughout the day or treatment cycle.

The invention will be further described with reference to the following non-limiting Examples.

Example 1

Subject 1: A 44 year old man exhibiting the symptoms of heart failure, including retention of body fluid manifested as moderate oedema of lower limbs and body fluid in the lungs. Also, moderate dyspnea and increased heart rate as well as an increase in liver size (indicative of fluid retention in the liver). Patient being treated for heart failure with lisinopril (Zestril®)

Treatment: 400 mg of a racemate of the Cis-2S,4R and Cis-2R,4S isomers of ketoconazole (Fungoral™ tablets - Janssen-Cilag, Belgium) was administered at 10.00 pm every day for a 3 month period.

Observations: Body weight reduced by 3.8 kg - attributable to a reduction in fluid retention.

Heart rate fell from 72 beats/min to 62 beats/min.

Reduction in liver size of 10% and a resulting reduction in liver transaminases
S-ASAT reduced from 0.44 to 0.30 μKat/L
S-ALAT reduced from 1.0 to 0.39 μKat/L

Dyspnea, oedema of lower limbs and body fluid in the lungs reduced.

Physical health as measured by a subnormal physical exercise test (Faggiano, P. et al. supra) improved by 15%.

Dose of lisinopril (Zestril®) could be reduced to half of original dose

Example 2

Subject 2: A 63 year old woman exhibiting the same symptoms of heart failure as subject 1. Patient being treated for heart failure with furosemid (40 mg/ day)

Treatment: As for Example 1.

Observations: Body weight reduced by 4.2 kg.

Heart rate fell from 74 beats/min to 60 beats/min.

Reduction in liver size of 15% and in liver transaminases.
S-ASAT reduced from 0.58 to 0.32 μKat/L
S-ALAT reduced from 0.92 to 0.68 μKat/L

Dyspnea, oedema of lower limbs and body fluid in lungs reduced.

Physical health, as measured by a subnormal physical exercise test, improved by 20%.

Dose of furosemid could be stopped within 6 weeks of commencement of treatment with ketoconazole.

Claims

1. Use of a cortisol antagonist in the manufacture of a medicament for the treatment of heart failure.

2. A use as claimed in claim 1 wherein the heart failure is categorised as congestive, diastolic, low-output or right-sided heart failure.

3. A use as claimed in claim 1 or claim 2 wherein the cortisol antagonist is an inhibitor of cortisol synthesis.

4. A use as claimed in claim 3 wherein the inhibitor of cortisol synthesis is ketoconazole or a derivative thereof.

5. A use as claimed in claim 4 wherein the cortisol synthesis inhibitor is the Cis-2S,4R and/or the Cis-2R,4S isomer of ketoconazole.

6. A use as claimed in any of the preceding claims wherein the medicament is for use in the treatment of enlargement of the heart or a fibrosis in the heart muscle.

7. Use of a cortisol antagonist in the manufacture of a medicament for the treatment of one or more symptoms associated with heart failure selected from the group comprising, oedema of lower limbs, pulmonary oedema, dyspnea, liver enlargement, increased heart rate, reduced stroke volume, shortness of breath and exercise intolerance.

8. A use as claimed in claim 7 wherein the medicament is for use in the treatment of pulmonary oedema.

9. A use as claimed in any one of the preceding claims wherein the daily dose of the cortisol antagonist to a patient being treated is 100-1200 mg.

10. A method of treating heart failure in a mammal which method comprises administering a pharmaceutically effective amount of a cortisol antagonist to said mammal.

11. A method of treating one or more symptoms associated with heart failure selected from the group comprising, oedema of lower limbs, pulmonary oedema, dyspnea, liver enlargement, increased heart rate, reduced stroke volume, shortness of breath and exercise intolerance in a mammal which method comprises administering a pharmaceutically effective amount of a cortisol antagonist to said mammal.

12. A product containing (a) a cortisol antagonist and (b) a second drug as a combined preparation for simultaneous, separate or sequential use in the treatment of heart failure or in improving cardiac function and reducing exercise intolerance.

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(54) Title: USE OF CORTISOL ANTAGONISTS IN THE TREATMENT FOR HEAT FAILURE

(57) Abstract: The present invention relates to the use of a cortisol antagonist in the manufacture of a medicament for the treatment of heart failure as well as to a method of treating heart failure which comprises administration of a cortisol antagonist and to a product containing (a) a cortisol antagonist and (b) a second drug as a combined preparation for simultaneous, separate or sequential use in the treatment of heart failure or in improving cardiac function and reducing exercise intolerance.

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COMBINED DECLARATION AND POWER OF ATTORNEY

(Original, Design, National Stage of PCT or CIP Application)

As a below named inventor, I hereby declare that:
My residence, post office address and citizenship are as stated below next to my name; I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

USE OF CORTISOL ANTAGONISTS IN THE TREATMENT OF HEART FAILURE

This declaration is of the following type:

[] Original
[] Design
[X] national stage of PCT/GB00/02551 (WO 01/01971), filed July 3, 2000.
[] Divisional
[] Continuation
[] Continuation-in-part (C-I-P)

the specification of which: *(complete (a), (b) or (c) for type of application)*

(a) [ ] is attached hereto.
(b) [X]was filed on December 28, 2001 as Application Serial No. 10/019613 and was amended on *(if applicable).*
(c) [ ] was described and claimed in International Application No. filed on and was amended on *(if applicable).*

Acknowledgment of Review of Papers and Duty of Candor

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the patentability of the subject matter claimed in this application in accordance with Title 37, Code of Federal Regulations § 1.56.

[] In compliance with this duty there is attached an information disclosure statement. 37 CFR 1.98.

Priority Claim

I hereby claim foreign priority benefits under Title 35, United States Code, § 119(a)-(d) of any foreign application(s) for patent or inventor's certificate or of any PCT International Application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT International Application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application on which priority is claimed

(complete (d) or (e))

(d) [ ] no such applications have been filed.
(e) [X] such applications have been filed as follows:

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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DATE	SIGNATURE OF INVENTOR			

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[ ] Signature for ninth and subsequent joint inventors. Number of pages added _____.

[ ] Signature by administrator(trix), executor(trix) or legal representative for deceased or incapacitated inventor. Number of pages added _____.

[ ] Signature for inventor who refuses to sign, or cannot be reached, by person authorized under 37 CFR 1.47. Number of pages added _____.

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Claim for Benefit of Prior U.S. Provisional Application(s)

I hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below:

Provisional Application Number	Filing Date

Claim for Benefit of Earlier U.S./PCT Application(s) under 35 U.S.C. 120

(complete this part only if this is a divisional, continuation or C-I-P application)

Application Serial Number	Filing Date	Status (patented, pending, abandoned)

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